UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,906	12/12/2001	Mark S. Chee	A-67991-3/RMS/DCF/KJC	3279

7590 04/08/2003

FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP
Suite 3400
Four Embarcadero Center
San Francisco, CA 94111-4187

EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,906	CHEE ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 27-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 27-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12 December 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

1. In the preliminary amendment filed on July 15, 2002, Applicants cancelled claims 1-26 and added new claims 27-42, which will be examined in this Office action.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

A) There is no reference to the parent application, 09/517,945, in the first paragraph of the specification.

B) In the declaration, Applicants claim priority to another non-provisional application 09/425,633. There is no specific reference to this application in the first paragraph of the specification.

C) In the first paragraph of the specification Applicants claim the benefit of the following provisional applications: 60/161,148; 60/135,051; 60/160,027 and 60/130,089, whereas in the declaration additional provisional applications are included: 60/135,053; 60/135,123; 60/160,927 and 60/160,917. There is no reference to these additional provisional applications in the first paragraph of the specification.

D) The provisional application number 60/160,027, filed on October 18, 1999, does not seem to have anything to do with Applicants' invention, since it's title is "CLOTHES DRYER WALL VENT BOX".

Information Disclosure Statement

3. The information disclosure statement filed on March 25, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Applicants did not provide references number 21-23, 25, 44-48, 87-89 and 93-95 neither in the parent application (09/517,945) nor in the recent submission, therefore these references were not considered.

Drawings

4. There are no separate descriptions of drawings 6A and 6B, and 7A-7F.

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: in Figures 4, 5A and 5B, the capture tag should have a reference sign "60" according to the specification, but it contains a reference sign "0-60". In Figure 4, a reference sign "70" is not described for this figure, and even though it is described for Figure 5A, it is not clear whether these two reference signs describe the same object. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 27-29 and 31-42 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 27 is drawn to a method of detecting an amplification reaction in which a primer is circularized by a first enzyme in the presence of a target nucleic acid and a circularized probe is contacted with a primer and a second enzyme to produce a concatamer amplicon.

Applicants provided a description of only one type of the first enzyme, a ligase, on page 4 (fourth paragraph), page 21 (second paragraph) and of only one type of the second enzyme, a polymerase, on page 4 (fourth paragraph), page 22 (fifth paragraph) and page 23 (first paragraph). Applicants did not provide any suggestions of what other enzymes could be used as the first and second enzymes. Applicants did not provide any examples of carrying out the method of claims 27-42.

Therefore, the application in it's current form does not contain a written description of the full scope of the claims.

8. Claims 27-29 and 31-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method which uses a ligase as the first enzyme and a polymerase as the second enzyme, does not reasonably provide enablement for all possible enzymes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 27 is drawn to a method of detecting an amplification reaction in which a primer is circularized by a first enzyme in the presence of a target nucleic acid and a circularized probe is contacted with a primer and a second enzyme to produce a concatamer amplicon. Therefore the scope of this claim encompasses all possible enzymes as the first and second enzymes, including all the enzymes whose activities have not yet been discovered.

Applicants provided a description of only one type of the first enzyme, a ligase, on page 4 (fourth paragraph), page 21 (second paragraph) and of only one type of the second enzyme, a polymerase, on page 4 (fourth paragraph), page 22 (fifth paragraph) and page 23 (first paragraph). Applicants did not provide any suggestions of what other enzymes could be used as the first and second enzymes. Applicants did not provide any examples of carrying out the method of claims 27-42.

The only known enzymes which join the ends of nucleic acids are proteins with ligase activity, and the only enzymes which amplify nucleic acids (i.e., create a copy of the template by extension of a primer) are proteins with polymerase activity. Therefore a skilled artisan would have to search for ligase or polymerase activity in any other enzymes which have nucleic acids as their substrates in order to determine which ones have such activities, as well as determine conditions under which such activities are manifested. Considering a number of all enzymes which have nucleic acids as their substrates it is a rather daunting task, requiring undue experimentation.

Due to the large quantity of experimentation necessary to determine which proteins beside ligases have ligase activity and which proteins beside polymerases have polymerase activity, the lack of direction/guidance presented in the specification regarding determination which proteins beside ligases have ligase activity and which proteins beside polymerases have polymerase activity, the absence of working examples directed to determination which proteins beside ligases have

ligase activity and which proteins beside polymerases have polymerase activity, undue experimentation would be required of the skilled artisan to use the invention in its full scope.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 27-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 27, 28, 29, 39, 41 and 42 are indefinite over the recitation of "circular primer". The term "circular" implies a molecule without free ends, whereas in claim 27 this circular primer is contacted with an enzyme which causes it to form a "circularized probe", implying that the primer had free ends, i.e., it was linear. Additional limitations for the "circular primer" in claims 28, 29, 41 and 42 refer to the primer's 5' and 3' ends, which cannot be present in a circular molecule.

B) Claim 27 is indefinite over the recitation of "contacting said hybridization probe with a first enzyme that causes modification of said circular primer to form a circularized probe". The only enzyme that will cause such modification (assuming that the "circular primer" has free ends) is a ligase, therefore it is not clear what other enzymes are encompassed by this limitation.

C) Claim 27 is indefinite over the recitation of "contacting said circularized probe with a first amplification primer and a second enzyme whereby a concatamer amplicon is formed". The only enzyme which can achieve amplification is a polymerase, and without it the method does not work, so it is not clear what other enzymes are encompassed by this limitation.

D) Claims 27 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the

elements. See MPEP § 2172.01. The omitted elements are: nucleotides which are required for extension of the primer by the polymerase.

E) Claims 28, 37 and 38 recites the limitation "said circular probe" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 27 contains a limitation "circularized probe".

F) The term "substantially complementary" in claim 40 is a relative term which renders the claim indefinite. The term " substantially complementary " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicants did not provide a definition of what "substantially complementary" means with respect to two nucleic acid sequences.

Priority date for claims 27-42

11. Applicants are notified that none of the provisional applications listed provides support for claims 27-42. Therefore the earliest priority date is March 3, 2000, the filing date of the parent application, 09/517,945.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 27-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Fan et al. (Publication US 2002/0006617 A1).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claim 27, Fan et al. teach a genotyping assay based on rolling circle amplification (RCA). A single target probe (RCA probe or padlock probe) is hybridized with a target nucleic acid, with each terminus of the probe hybridizing to adjacent portions of the target. The probe is circularized by ligation and amplified in the presence of a polymerase and a primer. The first end of the probe is substantially complementary to a first target domain and the second end is substantially complementary to a second target domain, which is adjacent to the first target domain ([0091], [0094], [0100]).

The probe contains a restriction site, which allows cleavage of the concatamers resulting from RCA amplification. Concatamers are cleaved into smaller fragments, which are then contacted with capture probes immobilized on microspheres (= beads). The capture probes on microspheres form an array. The digested fragments can be detected in two ways: either labeled nucleotides are incorporated during the amplification step or an additional labeled probe can be used ([0098], [0102]).

Fan et al. teach ordered and random arrays ([0152], [0179], [0180]). Microspheres are distributed in discrete sites on a substrate ([0156]- [0162]).

Regarding claims 28, 29, 41 and 42, Fan et al. teach that the first and second target domains may be directly adjacent or separated by one or more nucleotides, in which case a polymerase and dNTPs are used to fill the gap. The target domain orientation (5' or 3') depends on the orientation of the complementary target sequence ([0031]). Fan et al. teach ligases ([0114], [0295]).

Regarding claim 30, Fan et al. teach a polymerase ([0091],[0304]).

Regarding claim 31, Fan et al. teach labeled nucleotides in the amplification reaction ([0095]).

Regarding claim 32, Fan et al. teach contacting concatamer with a restriction enzyme ([0098], [0102]).

Regarding claim 33, Fan et al. teach wells ([0157]).

Regarding claim 34, Fan et al. teach a fiber optic bundle as a substrate ([0156]).

Regarding claim 35, Fan et al. teach substrates being glass or plastic ([0154]).

Regarding claim 36, Fan et al. teach random distribution of microspheres on the array ([0179], [0180]).

Regarding claim 37, Fan et al. teach the RCA probe comprising an adapter sequence ([0097]).

Regarding claim 38, Fan et al. teach the RCA probe containing a restriction site ([0098]).

Regarding claim 39, Fan et al. teach an RCA probe comprising a first and second target specific portions ([0096]), an amplification priming site ([0100]), an adapter sequence ([0097]) and a restriction site ([0098]).

Regarding claim 40, Fan et al. teach adapter sequences complementary to capture probes ([0022]).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 27-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor (Publication No. US 2002/0168645 A1) and Walt et al. (U.S. Patent No. 6,023,540).

A) Regarding claims 27, 28, 30 and 41, Taylor teaches detection of nucleic acid using rolling circle amplification. The method comprises hybridizing a single-stranded circular template (= circularized probe) to a sample (= target) nucleic acid, where the circular template has at least one sequence complementary to the target and at least one oligonucleotide which results in a cleavage site in an oligonucleotide multimer (= concatamer), followed by addition of a primer, dNTPs and a polymerase to produce an oligonucleotide multimer, cleavage of the multimer to produce cleaved amplified nucleic acid (= amplicon cleavage products), and contacting the cleavage products with an array of capture probes to detect the amplification products ([0005]-[0011], [0121]).

The circularized probe is prepared by hybridizing each end of a linear oligonucleotide (= circular primer) to a sample sequence, in such a way that a 3' end of the linear oligonucleotide has a sequence complementary to the 5' end of the target and the 5' end of the linear oligonucleotide has a sequence complementary to the 3' end of the target, and the 5' and 3' ends of the linear oligonucleotide are immediately adjacent to each other, followed by joining the ends of the linear oligonucleotide to form a circularized probe ([0012]-[0014]).

Taylor teaches an extension reaction catalyzed by a polymerase, a linking reaction catalyzed by a ligase and a nucleic acid cleavage reaction catalyzed by a restriction enzyme ([0036]).

Regarding claims 29 and 37-40, Taylor teaches an RCA probe with an interrogation region at its 5' end, which is complementary to an interrogation sequence (= detection position) on the target, and a terminal sequence at its 3' end, complementary to the probe annealing sequence of the target (Fig. 1; [0153-0156], [0164]) . The interrogation sequence may contain a polymorphic region, such as a single nucleotide polymorphism (SNP). The interrogation sequence can be positioned at the 3' end of the probe ([0168]). Taylor teaches an RCA probe comprising a restriction endonuclease site ([0159], Fig. 1), a tag sequence (= adapter), which can be used to hybridize the amplified product to a capture probe on the array ([0161], [0162], Fig. 1), and an RCA primer sequence (= amplification priming site), which allows priming of rolling circle amplification ([0163], Fig. 1).

Regarding claim 31, Taylor teaches RCA amplification with labeled nucleotides ([0169]).

Regarding claim 32, Taylor teaches cleavage of the concatamer amplicon with a type II S restriction endonuclease ([0170]).

Regarding claim 33, Taylor teaches arrays on microtiter plates with wells ([0121]).

Regarding claim 35, Taylor teaches substrate of glass or plastic ([0122]).

B) Taylor does not teach capture probes attached to microspheres which are randomly distributed on a surface of a substrate, or a substrate being a fiber optic bundle.

C) Regarding claims 27, 34 and 36, Walt et al. teach a microsphere-based analytical system with microspheres carrying different chemical functionalities and positioned in wells of a fiber optic bundle sensor. The population of beads includes separate subpopulations carrying different chemical functionalities (Col. 3, lines 18-31; col. 4, lines 4-15). The microbeads are randomly

distributed in an array (col. 4, lines 9-14). Each microsphere subpopulation contains different reporter dye, which may be fluorescent (col. 5, lines 40-52). The functionalites attached to the microspheres can be oligonucleotide probes (capture probes) (col. 10, lines 4-17, Table V).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to perform the nucleic acid detection methods of Taylor on an array of Walt et al. The motivation to do so, provided by Walt et al., would have been that fiber-optic sensor supported a large number of chemical functionalities and was easy to use and manufacture.

16. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor and Walt et al. as applied to claim 27 above, and further in view of Lizardi (U.S. Patent No. 5,854,033; cited in the IDS).

A) Claim 42 is drawn to the circular primer hybridizing to target nucleic acid in such a way that it's 5' end and 3' end are not immediately adjacent and contacting the hybridization complex with a polymerase which fills the gap between the two ends of the primer.

B) Taylor teaches a probe which has the 5' and 3' ends immediately adjacent to each other upon binding to the target, but does not teach a gap between the ends of the probe.

C) Lizardi teaches an open circle probe which can bind to the target nucleic acid in such a way that it's 5' and 3' ends are separated by a gap, which can then be filled by a polymerase (col. 5, lines 25-28; col. 6, lines 39-46; Fig. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used a probe of Lizardi in the combined method of Taylor and Walt et al. The motivation to do so, provided by Lizardi, would have been that using gaps between the ends of the probe allowed amplification of different allelic variants of the target sequence.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Fan et al., US 2002/0132241 A1.
- Fan et al., US 2002/0172946 A1.
- Fan et al., US 2003/0003490 A1.
- Mahtani, US 6,221,603 B1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

April 7, 2003

Teresa Strzelecka

Patent Examiner

Teresa Strzelecka
4/7/03